REMARKS

Claim Amendments

Claims 1-18, which were previously withdrawn as being directed to a non-elected invention, have been canceled. Applicants reserve the right to pursue the subject matter of Claims 1-18 in a continuation or divisional application.

Claims 19, 24 and 29 have been amended to recite "wherein the immunogenic mutant or fragment maintains the function of peptide 165 as a CD8 T cell epitope of the vaccinia or variola virus". Support for this amendment can be found, for example, at page 14, lines 28-29 and page 15, lines 15-25 of the specification.

Claims 19, 24 and 29 have been amended further to recite "a vaccinia or variola virus that comprises a polypeptide having an amino acid sequence that is identical or substantially homologous to peptide 165 (SEQ ID NO: 2)" (Claims 19 and 24) or "a vaccinia vaccine that comprises a polypeptide having an amino acid sequence that is identical or substantially homologous to peptide 165 (SEQ ID NO: 2)" (Claim 29). Support for these amendments can be found, for example, at page 18, lines 8-15 of the specification.

Claim 30 has been amended to correct a typographical error.

The amended claims are supported by the subject application as originally filed.

Elections/Restrictions

In the Office Action, the Examiner states that "Applicants are reminded to amend claims to the elected scope for reflecting the examination on the record" (Office Action, page 2).

Applicants have amended Claims 19, 24 and 29, accordingly, to delete recitations of non-elected subject matter.

Rejection of Claims 19-34 under 35 U.S.C. §112, second paragraph

Claims 19-34 are rejected under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 2). In particular, the Examiner states that "the metes and

bounds of 'an immunogenic mutant or fragment thereof' are not defined" in claims 19, 24 or 29, or in the specification of the subject application (Office Action, page 2).

Applicants respectfully disagree. In the specification as filed, Applicants clearly teach that "[p]eptide 74A and peptide 165 of the invention are CD8 epitopes" (specification, page 14, line 28) and that "the terms 'immunogenic fragment' and 'mutant' of peptide 74A and/or peptide 165 refer to polypeptides in which 1 to about 4 amino acids have been substituted without essentially detracting from the immunological properties thereof" (specification, page 15, lines 15-18; emphasis added). Thus, the specification contains a clear and explicit definition of the terms "immunogenic mutant" or "fragment thereof". Nevertheless, to define the claimed subject matter more clearly and distinctly, Applicants have amended Claims 19, 24 and 29, from which the other rejected claims depend, to recite "wherein the immunogenic mutant or fragment maintains the function of peptide 165 as a CD8 T cell epitope of the vaccinia or variola virus". Therefore, Claims 19-34, particularly as amended, are both clear and definite.

Rejection of Claims 19-34 under 35 U.S.C. §112, first paragraph

Claims 19-34 are rejected under 35 U.S.C. §112, first paragraph, because it is the Examiner's opinion that the specification does not enable one of skill in the art to use peptide 165 to activate any population of T cells that were previously exposed to any vaccinia or variola virus or their vaccine, nor does the specification enable one of skill in the art to use any antigenic mutant or fragment of any vaccinia or variola virus to activate any population of T cells (see Office Action, page 3).

Specifically, the Examiner asserts that the specification does not enable "using any antigenic mutant or fragment" of SEQ ID NO: 2 "to activate any population of T cells" that were "previously exposed to any or all vaccinia virus or viola [sic] virus or a vaccine thereof" (see Office Action, pages 3). The Examiner further states that "the broad reasonable interpretation of a mutant or a fragment of peptide of SEQ ID NO: 2 can read on as small as a peptide containing only one or two amino acid residues derived from the SEQ ID NO: 2" (Office Action, page 4).

Applicants respectfully disagree. The pending claims must be given their broadest reasonable interpretation consistent with the specification (*In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000)). As noted above, in the specification as filed, Applicants

teach that "[p]eptide 74A and peptide 165 of the invention are CD8 epitopes" (specification, page 14, lines 28-29) and that "the terms 'immunogenic fragment' and 'mutant' of peptide 74A and/or peptide 165 refer to polypeptides in which 1 to about 4 amino acids have been substituted without essentially detracting from the immunological properties thereof" (specification, page 15, lines 15-18; emphasis added). Furthermore, the amino acid sequences of several suitable immunogenic mutants of peptide 165 are provided in Table 2 of the specification (specification, page 16, lines 1-21). Nevertheless, Applicants have amended Claims 19, 24 and 29, from which the other rejected claims depend, to state that the recited immunogenic mutant or fragment thereof "maintains the function of peptide 165 as a CD8 T cell epitope of the vaccinia or variola virus".

The Examiner further asserts that "[t]he specification does not teach how to select or produce said mutant or fragment of SEQ ID NO: 2" (Office Action, page 4).

Applicants respectfully disagree. With knowledge of the amino acid sequence of SEQ ID NO: 2, which Applicants disclose in the specification, one of skill in the art clearly would be able to produce fragments of this nine amino acid peptide (e.g., a seven amino acid fragment consisting of seven consecutive amino acid residues of SEQ ID NO: 2), wherein the fragment functions as a CD8 T cell epitope of a vaccinia or variola virus, using routine skills and techniques (e.g., direct chemical synthesis, peptidase-mediated cleavage of SEQ ID NO: 2). Moreover, one of skill in the art clearly would be able to produce mutants of SEQ ID NO: 2 that differ from SEQ ID NO: 2 only by the presence of 1 to 4 substituted amino acids, wherein the mutants retain the immunogenic properties of SEQ ID NO: 2 (e.g., function as a CD8 T cell epitope), using standard procedures and techniques. For example, in the specification as filed, Applicants teach that

> *in vitro* mutagenic techniques can be used to modify the cloned gene encoding peptide 74A and/or peptide 165. Such methods, which are well known to one skilled in the art, can be used to delete, insert or substitute nucleotides in the gene resulting in the deletion, insertion or substitution of amino acids in the encoded product. Examples of immunogenic fragments or mutants of peptide 74A and peptide 165 include, but are not limited to, those shown in Table 2. The immunological properties of the mutagenized encoded product can be assayed using methods such as those which are well known to one skilled in the art.

(specification, page 15, lines 18-25). As Applicants point out in the specification, such methods include a cytokine assay (*e.g.*, ELISPOT), a flow cytometry assay (*e.g.*, tetramer staining assay), intracellular cytokine staining assay (ICS) and/or a limiting dilution assay (LDA) (specification, page 20, lines 24-27).

The Examiner also states that "it is unpredictable whether said smallpox peptide of SEQ ID NO: 2 can stimulate any or all T cells that are previously exposed to any or all vaccinia viruses" and that "it is very unpredictable whether any mutant or fragment of SEQ ID NO: 2 will have the same biological activity" as required for claims 19-34 (Office Action, page 4).

While disagreeing with the Examiner, Applicants have amended Claims 19, 24 and 29, from which the other rejected claims depend, to clarify that the recited vaccinia or variola virus (Claims 19 and 24), or the recited vaccinia vaccine (Claim 29), "comprises a polypeptide having an amino acid sequence that is identical or substantially homologous to peptide 165 (SEQ ID NO: 2)". Thus, the instant claims, particularly as amended, are directed to methods that are applicable to any vaccinia and/or variola virus or vaccine that comprises a polypeptide having an amino acid sequence that is identical or substantially homologous to peptide 165 (SEQ ID NO: 2). Several examples of such viruses are disclosed in Table 1 of the specification (specification, page 9, lines 10-25).

In the Office Action, the Examiner asserts that "[t]he specification only teaches to use peptide of SEQ ID NO: 2 to activate the smallpox pre-exposed cells," that "[t]he specification does not teach how to select or produce said mutant or fragment of SEQ ID NO: 2" and that "[t]he specification does not teach that said peptide is able to active [sic] any or all vaccinia virus pre-exposed T cells" (Office Action, page 4).

Applicants respectfully disagree. As discussed above, Applicants' specification is fully enabling for producing mutants and fragments of SEQ ID NO: 2 that maintain the function of SEQ ID NO: 2 as a CD8 T cell epitope. In the specification as filed, Applicants clearly teach that

> Whether the T cells present in the sample become activated can be determined using a variety of assays known to those of skill in the art. For example, a cytokine assay (*e.g.*, ELISPOT), a flow cytometry assay (*e.g.*, tetramer staining assay), intracellular cytokine staining assay (ICS) and/or a limiting dilution assay (LDA) can be used in the methods of the present invention.

(specification, page 20, lines 23-27).

Thus, the instant specification provides sufficient guidance regarding how to select and produce an immunogenic mutant or fragment of peptide 165 (e.g., *in vitro* mutagenesis techniques, molecular cloning, chemical synthesis) and how to test whether said immunogenic mutant or fragment can activate T cells in a sample, using routine assays and procedures (e.g., ELISPOT assay, tetramer staining assay, ICS assay, LDA assay). Therefore, one of skill in the art would be able to practice the claimed methods using the guidance provided by Applicants in the specification as filed, and standard reagents, techniques and protocols.

Accordingly, Applicants' specification is enabling for the full scope of the claimed invention, particularly as amended.

Double Patenting Rejection of Claims 19-34

Claims 19-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28-43 of copending Application No. 11/238,122 (Office Action, page 6). According to the Examiner, "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the conflict claims have overlapping scopes" (Office Action, page 6).

Once the present claims of the subject application are deemed allowable, Applicant will submit a terminal disclaimer if the allowable claims cover subject matter that is not patentably distinct from the subject matter covered by the claims of U.S. Patent Application No. 11/238,122. A terminal disclaimer is not an admission or comment regarding the merits of the rejection (*Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991)).

Rejection of Claims 19-34 under 35 U.S.C. §102(a)

Claims 19-34 are rejected under 35 U.S.C. §102(a) "as being anticipated by Drexler et al (PNAS January 2003, Vol. 100, No. 1, pp. 217-222)" (Office Action, page 6). According to the Examiner, "Drexler et al. teach a method for activating a population of T cells isolated from the vaccinia virus immunized mouse using a HLA-A 0.021 -restricted T cell epitope containing peptide" (Office Action, page 7). The Examiner asserts that "[b]ecause the claimed mutant does

not have any structural limitation", all peptides disclosed in the prior art can be considered mutants of the claimed peptide 165 (Office Action, page 7).

Applicants respectfully disagree. As amended, Applicants' invention is directed to methods comprising determining whether T cells become activated in the presence of a polypeptide selected from the group consisting of: peptide 165 (SEQ ID NO: 2), an immunogenic mutant or fragment of SEQ ID NO: 2 that maintains the function of peptide 165 as a CD8 T cell epitope of a vaccinia or variola virus, and a combination thereof.

Anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference (*Akzo N.V. v. International Trade Comm.*, 11 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986)). Drexler *et al.* (PNAS January 2003, Vol. 100, No. 1, pp. 217-222) disclose "an immunodominant HLA-A*0201-restricted vaccinia virus-specific peptide epitope, VP35#1, which is encoded by the vaccinia virus gene H3L and can be recognized by murine and human $CD8^+$ T cells" (Drexler *et al.*, page 217, right column). Drexler *et al.* teach that the amino acid sequence of VP35#1 is SLSAYIIRV (Drexler *et al.*, page 219, Fig. 1A). Notably, Drexler *et al.* do not disclose a peptide consisting of either SEQ ID NO: 2, a fragment of SEQ ID NO: 2, or an immunogenic mutant of SEQ ID NO: 2, as defined in the instant specification. Therefore, Drexler *et al.* clearly do not teach Applicants' claimed methods, particularly as amended.

Rejection of Claims 19-34 under 35 U.S.C. §102(a)

Claims 19-34 are rejected under 35 U.S.C. §102(a) "as being anticipated by Drexler et al (EP 1, 398,380A1)" (Office Action, page 7). According to the Examiner, "Drexler et al. teach a method for detecting a T cell response induced by smallpox vaccines in human comprising [sic] contacting a sample containing T cells . . . and co-culturing said sample with one or more peptides that contain [an] HLA-A 0201 restricted epitope, which is considered as [a] variant or mutant of the claimed peptide 165" (Office Action, page 7). The Examiner asserts that "[b]ecause the claimed mutant does not have any structural limitation", all peptides disclosed in the prior art can be considered mutants of the claimed peptide 165 (Office Action, page 8).

Applicants respectfully disagree. As stated above, Applicants' invention, particularly as amended, is directed to methods comprising determining whether T cells become activated in the presence of a polypeptide selected from the group consisting of: peptide 165 (SEQ ID NO: 2), an

immunogenic mutant or fragment of SEQ ID NO: 2 that maintains the function of peptide 165 as a CD8 T cell epitope of a vaccinia or variola virus, and a combination thereof.

Anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference *(Akzo N.V. v. International Trade Comm.*, 11 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986)). Drexler *et al.* (EP 1,398,380 A1) teach "a method of detecting a T cell response induced by smallpox vaccines or Orthopoxvirus vector vaccines in a mammal" (Drexler *et al.*, page 2, lines 3-4). Furthermore, Drexler *et al.* disclose the amino acid sequences of several HLA-A*0201-restricted peptide-epitopes derived from vaccinia virus-encoded proteins (Drexler *et al.*, Fig. 1, page 23). Notably, Drexler *et al.* do not disclose a peptide consisting of either SEQ ID NO: 2, a fragment of SEQ ID NO: 2 or an immunogenic mutant of SEQ ID NO: 2, as defined in the instant specification. Therefore, Drexler *et al.* do not teach Applicants' claimed methods, particularly as amended.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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Dated: September 29, 2006